

REVIEW

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Combination of probenecid-sulphadoxine-pyrimethamine for intermittent preventive treatment in pregnancy

Julie Gutman^{1*}, S Patrick Kachur¹, Laurence Slutsker², Alexis Nzila³ and Theonest Mutabingwa⁴**Abstract**

The antifolate sulphadoxine-pyrimethamine (SP) has been used in the intermittent prevention of malaria in pregnancy (IPTp). SP is an ideal choice for IPTp, however, as resistance of *Plasmodium falciparum* to SP increases, data are accumulating that SP may no longer provide benefit in areas of high-level resistance. Probenecid was initially used as an adjunctive therapy to increase the blood concentration of penicillin; it has since been used to augment concentrations of other drugs, including antifolates. The addition of probenecid has been shown to increase the treatment efficacy of SP against malaria, suggesting that the combination of probenecid plus SP may prolong the useful lifespan of SP as an effective agent for IPTp. Here, the literature on the pharmacokinetics, adverse reactions, interactions and available data on the use of these drugs in pregnancy is reviewed, and the possible utility of an SP-probenecid combination is discussed. This article concludes by calling for further research into this potentially useful combination.

Keywords: Malaria, Sulphadoxine-pyrimethamine, Probenecid, Pregnancy**Background****Decreasing efficacy of sulphadoxine-pyrimethamine for intermittent prevention of malaria in pregnancy**

The antifolate sulphadoxine-pyrimethamine (SP) has been used in the intermittent prevention and treatment of malaria in pregnancy; in addition, it has been explored for intermittent preventive treatment (IPT) in infants and children [1-7]. SP is an ideal choice for intermittent preventive treatment in pregnancy (IPTp), as it is effective as a single dose given two to three times in pregnancy, with an interval of at least one month between doses. Data from Mali suggest that three doses are significantly more effective than two doses [8]. Resistance of *Plasmodium falciparum* to SP has been increasing, and its use is no longer recommended for treatment of malaria in Africa [9-11]. In some areas where SP is no longer an effective malaria therapy, IPTp with SP has been shown to be beneficial to HIV-uninfected pregnant women, possibly as a result of their pre-existing immunity [1]. Of concern,

however, is a recent report from Muheza, an area of Tanzania with high level SP resistance, suggesting that its use for IPTp may exacerbate resistance [12]. In that study, SP-IPTp was associated with a 5.4% increase ($p = 0.003$) in the prevalence of parasitaemia in women who reported SP-IPTp use compared to those who did not. In addition, women who reported SP-IPTp use had both a higher prevalence of placental inflammation by histopathology and higher intensity of inflammation than women who did not report using SP-IPTp [12]. A subsequent study from the same area showed the lack of beneficial pregnancy outcomes from SP-IPTp [13]. Data from Malawi also show that the effectiveness of SP-IPTp has been decreasing over time and no longer appears to provide any benefit [14]. In view of these findings, it is critical to search for new agents for IPTp; mefloquine or azithromycin-based combinations (including azithromycin plus chloroquine) currently appear most promising [15]. While searching for alternatives to SP-IPTp, data from in vitro experiments have shown that probenecid can increase the activity of the anti-malarial antifolates [16,17]. Furthermore, malaria treatment studies in Nigerian children have shown that the addition of probenecid

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increases the treatment efficacy of SP [18,19]. Implicitly, the combination of probenecid plus SP may prolong the useful lifespan of SP as an effective agent for IPTp.

Mechanism of action and development of resistance to SP

Sulphadoxine and pyrimethamine act synergistically to inhibit two steps in the folate synthesis pathway. Sulphadoxine inhibits the enzyme dihydropteroate synthetase (*dhps*) while pyrimethamine inhibits the enzyme dihydrofolate reductase (*dhfr*). Resistance develops in a step-wise manner due to a combination of mutations in these genes, with increasing numbers of mutations conferring increasing levels of resistance [20]. This results in an increased minimal inhibitory concentration (MIC), which translates to a decreased duration of prophylaxis because as drug levels fall, they reach the point at which they no longer suppress parasite replication sooner (Figure 1) [21]. The presence of the “quintuple mutant” consisting of the *dhfr* triple mutant (point mutations causing a Ser → Asn change at position 108, Asn → Ile at codon 51, and Cys → Arg at codon 59) and the *dhps* double mutant (due to point mutations which convert Ala → Gly at codon 437 and Lys → Glu at codon 540) has been most strongly associated with treatment failure [22], although host immunity still plays a significant role in determining drug efficacy [23]. Although theoretically, increasing the dose of SP could potentially overcome resistance to some degree, modelling suggests that increasing the dose of SP dose will only have a marginal benefit since highly resistant parasites will not be efficiently cleared by in vivo drug levels achievable within safety margins [24]. Furthermore, data in pregnant women indicate that there is significant

variability in the effect of pregnancy on the disposition of SP, thus it was concluded that it is not possible to recommend an adjustment to the dose of SP to increase its efficacy [25].

Rationale for use of probenecid

Probenecid was developed in 1950 to inhibit the renal tubular secretion of penicillin, increasing the blood concentration of the drug and decreasing the required dose [26,27]. Since its introduction, it has been found to inhibit the tubular secretion of other weak organic acids, such as p-aminohippuric acid, salicylic acid and uric acid, as well as other antibiotics (including cephalosporins), and anti-retrovirals (including oseltamavir and zidovudine). This characteristic of probenecid allows for decreased doses of medications to be used, thus limiting toxicity, especially with nephrotoxic agents [27-30]. Probenecid has been widely used as an uricosuric agent in the treatment of gout [26], and has a long history of use without serious toxicity [31]. It is widely available and inexpensive, costing approximately US\$1 per 500 mg tablet.

Probenecid is a substrate for multi-drug resistance-associated protein (MRP) and the uric acid transporter [32] and is an inhibitor of both organic anion transporters 1 and 3 (OAT1 and OAT3) [33-35]. Probenecid increases plasma concentrations of the antifolate methotrexate by inhibiting drug efflux mediated by the MRP family of ATP-binding cassette transporters while at the same time inhibiting folate uptake [36]. This has been shown to reverse some forms of methotrexate resistance, and can increase the anti-cancer efficacy of anti-folate drugs (methotrexate analogs) [36,37].

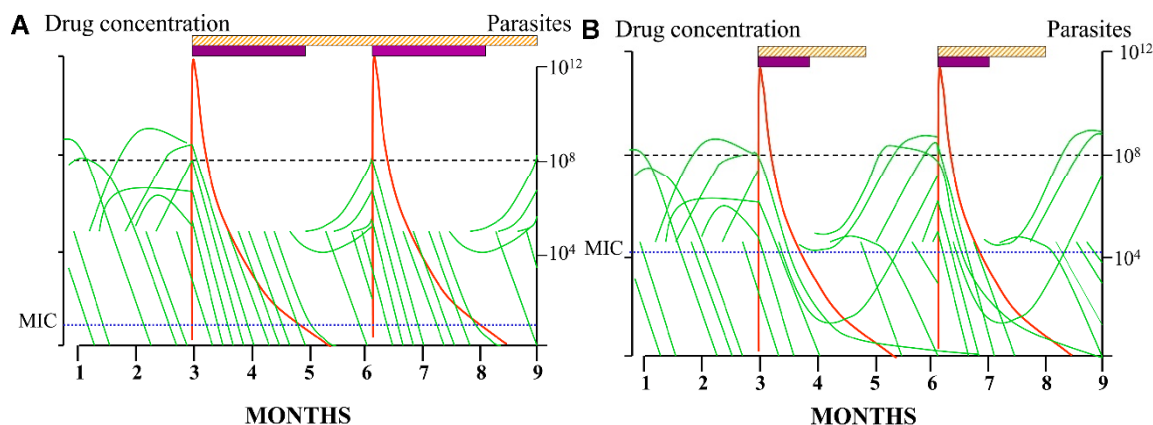


Figure 1 Hypothetical parasite burden profiles during pregnancy with SP IPT in a high-transmission setting. Entomological inoculation rate is about 50 infectious bites per person per year. Note that many infections self-cure (each infection is depicted as a green line). The hatched bars represent the duration of “suppressive prophylactic activity”, and the solid bars represent the period during which parasite multiplication is suppressed (i.e. levels exceed the in vivo MIC). The horizontal dotted line at 10^8 parasites represents the level at which malaria can be detected on a blood film. (A) represents a drug-sensitive area; (B) represents a moderately resistant area. Reproduced from: White NJ (2005) Intermittent Presumptive Treatment for Malaria. *PLoS Med* 2(1): e3. doi:10.1371/journal.pmed.0020003

For treatment of *P. falciparum* infections, studies have clearly demonstrated that the addition of folate derivatives decreases the activity of antifolate drugs, both in vitro and in vivo [38-40]. Likewise, the lowering of folate concentration in vivo enhances the activity of antifolate anti-malarial agents [41]. This, taken together with the data from the studies of methotrexate, suggests that probenecid may be able to increase the efficacy of antifolates against resistant *Plasmodium* parasites by increasing the concentration of drug and limiting the uptake of folate. This has been demonstrated in vitro for the antifolates sulphadoxine, dapsone, pyrimethamine, and chlorcycloguanil [17]. In the presence of clinically achievable probenecid concentrations (50 μ M or 14.268 mcg/ml), the activity of these antifolates was significantly increased. Increased activity ranged from two- to seven-fold, and in the case of resistant parasite isolates, reduced half maximal inhibitory concentrations (IC_{50}) to levels seen in drug sensitive isolates [17]. These improvements in drug susceptibility correlated with reduced folate uptake in the presence of probenecid [17]. Probenecid has also been shown to reverse chloroquine resistance and increase piperaquine activity in vitro [17,42].

Probenecid has been shown to increase the efficacy of SP for the treatment of malaria in clinical trials in Nigerian children in an area with approximately 25% resistance to SP. In a study of 151 children under the age of 12 years, Sowunmi et al. showed that the addition of approximately 20-25 mg/kg/d of probenecid for three-days to standard SP dosing increased the efficacy of SP, as measured by the parasitological cure rate at day 14, compared to children who received SP alone (96.2% vs 83.5%, $p = 0.02$, $n = 78$ and 73, respectively) [19]. Although the cure rate in the SP-probenecid group remained higher at day 28, this was no longer statistically significant (79.4% vs 72.6%, $p = 0.4$) [19]. The combination of SP-probenecid was well tolerated in this small study and had no significant side effects [19]. Similar findings were reported from the same study population, with a 14-day cure rate of 100% in the SP-probenecid arm ($n = 5$) compared to 88% in the SP arm ($n = 25$) in one study and 94.8% ($n = 39$) compared to 76.4% ($n = 34$, $p = 0.02$) in another [18,43].

Although probenecid has been in use for over half a century, and has been recommended as part of the treatment of gonorrhea in pregnancy, very little clinical data exist on its safety in pregnancy. Furthermore, no clinical studies have been done on the pharmacokinetics of probenecid in pregnancy. Available evidence suggests that probenecid may potentiate the effect of SP and thus prolong its use for IPTp. However, data from pregnant women are needed to explore this potential. This review presents available data and highlights the knowledge

gaps surrounding potential use of SP-probenecid combination as an effective agent for IPTp.

Pharmacokinetics

Probenecid

Probenecid is packaged as 500 mg tablets. It is a weak acid (pKa 3.7) [44], and its oral bioavailability is > 90% [45]. In healthy adults, probenecid is 85-95% bound to plasma albumin and has a small apparent volume of distribution of 0.003-0.014 L/kg [44,46]. The maximum adult dose of probenecid is 3 g, and a single oral dose of 2 g (approximately 25 mg/Kg) yields peak plasma concentrations of 150-200 mcg/mL within four hours; concentrations above 50 mcg/mL are sustained for eight hours [31,47]. Following a 2 g dose, the half-life is 4-17 h; the half-life is dose-dependent, decreasing as the dose decreases to 500 mg [31]. Probenecid is metabolized in the liver via oxidation and glucuronidation and is primarily excreted in the urine (75-85%) [27]. No dosage adjustment is necessary for patients with mild renal failure (glomerular filtration rate greater than 50 mL/min); probenecid is not effective in severe renal failure and should be avoided [48,49]. No data are available on the pharmacokinetics of probenecid in pregnant women.

Sulphadoxine-pyrimethamine (SP)

SP is packaged as a fixed dose combination containing 500 mg sulphadoxine and 25 mg pyrimethamine and costs approximately US\$1 per treatment (adult dosage is three tablets). In the non-pregnant population, both sulphadoxine and pyrimethamine have an oral bioavailability of > 90%, and are 85-90% protein bound [25]. The volume of distribution for sulphadoxine and pyrimethamine is 0.14 L/kg and 2.3 L/kg, respectively [50]. Oral administration of one tablet yields peak plasma levels of approximately 0.2 mg/L for pyrimethamine and approximately 60 mg/L for sulphadoxine at approximately four hours [50]. Both compounds have a very long half-life; the half-life of sulphadoxine is approximately 169 h (range 100-230 h), while that of pyrimethamine is approximately 111 h (range 54-148 h) [51]. Sulphadoxine is metabolized via glucuronidation and excreted primarily in urine, while pyrimethamine is metabolized to several unidentified metabolites but also excreted primarily in the urine [25,52].

Several studies have examined the pharmacokinetics of SP in pregnant women. All examined the standard dose for IPTp of three tablets (1500 mg of sulphadoxine and 75 mg of pyrimethamine). Nyunt et al. studied women in four African countries both during pregnancy and six to eight weeks post-partum, and found that, at Day 7 following administration of SP, there was an increased blood concentration of pyrimethamine, with an area under the curve (AUC) of 1,906 ng-day/ml during pregnancy vs 849 ng-day/ml postpartum, with geometric

mean ratio of pharmacokinetic values between pregnancy and postpartum period 1.38 (1.22-1.56), p -value < 0.0001. In addition, they found decreased concentration of sulphadoxine with an AUC of 877 $\mu\text{g}\cdot\text{day}/\text{ml}$ during pregnancy versus 884 $\mu\text{g}\cdot\text{day}/\text{ml}$ postpartum, with geometric mean ratio of pharmacokinetic values between pregnancy and postpartum period 0.88 (0.80-0.96), p -value = 0.004, also on Day 7. However, there was significant variation in the exact pharmacokinetic parameters among the different study sites [25]. Findings from a study done in Kisumu, Kenya by Green et al., looking at levels of SP during pregnancy compared to eight-12 weeks post-partum, found similar results for sulphadoxine [53]. However, pyrimethamine pharmacokinetics were not significantly different in pregnant vs non-pregnant women [53]. In a third study conducted in Papua New Guinea where pregnant women were matched to non-pregnant controls, plasma concentrations of both sulphadoxine and pyrimethamine were found to be lower in the pregnant women compared to the non-pregnant controls (AUC of 22,315 vs 33,284 $\text{mg}\cdot\text{h}/\text{l}$ for sulphadoxine and 72,115 vs 106,065 $\mu\text{g}\cdot\text{h}/\text{l}$ for pyrimethamine; p -value < 0.001 for both) [54]. These varying results may be due to genetic differences in the women that contribute to differential drug metabolism, as well as to differences in body weight.

There are no data on how the combination of probenecid, sulphadoxine, and pyrimethamine affects pharmacokinetics or pharmacodynamics of the individual drugs. Further studies are needed to define these effects and to determine optimal dosing regimens. Given the significant differences in the half lives of SP and probenecid, there is also a need to optimize the probenecid regimen to maximize efficacy of SP while minimizing the frequency of administration to facilitate adequate compliance and adherence.

Adverse events

Probenecid

Adverse reactions with probenecid are quite rare, occurring in approximately 0.1-0.3% of the general population, although the rate in pregnancy is unknown [55]. While rare, adverse reactions have been reported in almost all organ systems, including gastrointestinal, dermatologic, hematologic, renal, and immunologic (anaphylaxis) [26]. Isolated cases of aplastic anaemia, leukopenia, neutropenia, and thrombocytopenia have been reported [56]. Early reports suggested that probenecid may be associated with haemolysis in individuals with glucose-6-phosphatase dehydrogenase (G6PD) deficiency [57]. However, this has not been shown to be the case in subsequent studies [58,59]. Furthermore, recent reviews report that probenecid is not likely to cause haemolysis in patients with G6PD deficiency [60,61].

Probenecid has, however, been associated with immune mediated haemolytic anaemia in several case reports [62,63]. Nephrotic syndrome, which typically resolves on removal of drug, has been reported in a very small number of cases, with one case progressing to death [64-68]. There has also been a single case report of fatal hepatic necrosis [69]. Hypersensitivity reactions to probenecid in the general population may occur in as many as 2% to 4%. The incidence of probenecid hypersensitivity is much higher in HIV-infected patients ranging from 11% to 25% [70]. These reactions ranged from a mild rash that resolved with continued drug administration to more severe reactions consisting of a diffuse rash accompanied by constitutional symptoms, including fever and hypotension, leading to discontinuation of the drug [71-73]. There has been a single case report of anaphylactoid reaction after a single oral dose of probenecid [74].

Sulphadoxine-pyrimethamine (SP)

Despite a long list of potentially severe side effects associated with sulphonamides, the dose of SP used for IPTp is generally well tolerated [50,51]. Bone marrow suppression including agranulocytosis, aplastic anaemia, megaloblastic anaemia, thrombocytopenia, leukopenia, haemolytic anaemia, and eosinophilia may be seen. Haematologic adverse events are related to folic acid antagonism, and can generally be reversed with folinic acid [51]. Mild adverse reactions, such as nausea, vomiting, rash, pruritus, and fatigue have been reported in a small proportion (1-2%) of patients following a single dose of SP [1,75-77]. Parise et al. reported an increased incidence of adverse events in women with HIV, but this was not confirmed in a study by Filler et al. [75,76]. Severe adverse events are rare [1]. Cutaneous hypersensitivity reactions (i.e. Stevens-Johnson syndrome and toxic epidermal necrolysis) are the most common severe adverse events. In studies of travellers taking weekly SP for malaria prophylaxis, the rate of cutaneous hypersensitivity reactions has been reported to be approximately one per 5,000-8,000, with one fatality per 11,000-25,000 [78-80]. The crude rate of cutaneous hypersensitivity reaction was reported to be approximately 1.2 per 100,000 exposures to SP in passive surveillance data from 22 health facilities in Blantyre, Malawi [81]. In that study, the rate of cutaneous hypersensitivity in HIV-infected individuals was approximately four times the crude rate, at 4.9 cases per 100,000 [81]. In a study comparing IPTp with standard SP to SP plus azithromycin, Luntamo et al. reported 14 maternal severe adverse events, including one maternal death, among 1,320 women (1%). However, the majority of these were considered to be unrelated to the study drugs [82]. It is unclear whether any of the reported adverse events were severe cutaneous reactions. In a systematic review of

IPTp-SP, ter Kuile et al. report a total of 21 maternal deaths among 11,379 doses of SP given to 4,911 women; nine of these occurred in women receiving placebo [1]. Only one of these deaths was reported to be due to a severe cutaneous hypersensitivity reaction, and it occurred in an HIV-positive woman three weeks after the dose of SP [1,77]. A more comprehensive review of cutaneous hypersensitivity reactions was conducted by Peters et al. [51]. Other, less common, severe reactions that have been seen with SP use include liver toxicity (e.g. cholestatic hepatotoxicity and fulminant hepatic necrosis), fever, and respiratory problems such as hypersensitivity pneumonitis [51]. Patients with G6PD deficiency can safely receive SP-IPTp or malaria treatment with SP [51,83].

Pregnancy

Probenecid

Probenecid is known to cross the placental barrier and appears in cord blood [48]. There are limited data on the use of probenecid in pregnancy, with approximately 460 cases described in the literature (Table 1). In most of these cases, no data are provided on the outcome of pregnancy. Of the few studies that describe foetal outcomes, none shows a statistically significant increase in foetal adverse events in infants exposed to probenecid compared to controls [84], although the small sample size of most of these studies is a major limitation to effectively evaluating infant outcomes. Due to the paucity of data, the US Food and Drug Administration classifies probenecid as Pregnancy Category B. However, the data available do not suggest any evidence of teratogenic effects of probenecid when used in pregnancy [48,55].

Sulphadoxine-pyrimethamine

SP is classified by the US Food and Drug Administration as belonging to Pregnancy Category C. Pyrimethamine is teratogenic at doses well above the standard human dose in rats, hamsters and miniature pigs; effects including foetal re-absorption, cleft palate, bradygnathia, oligodactyly, and microphthalmia have been seen [50]. Sulphadoxine is also teratogenic in rats [50]. In rabbits, no teratogenic effects were noted at oral doses as high as 20 mg/kg pyrimethamine plus 400 mg/kg sulphadoxine [50]. One large study in humans looking at the effect of folic acid antagonists found an increased risk of malformations, including cardiovascular defects, oral clefts, and urinary tract defects, with exposure in the first trimester, but not in subsequent trimesters [91]. However, several large studies of SP-IPTp, including several randomized controlled trials, have not found an association between the use of SP and congenital anomalies [67,68]. Therefore, despite data suggesting teratogenicity in certain animal models, there is a large body of evidence

suggesting that SP-IPTp is safe for use in humans during the second and third trimesters. Of note, probenecid in combination with SP would potentiate the antifolate effect of SP [36], with the potential danger of reducing the folates available to the growing foetus. Therefore, should this combination be adopted, careful monitoring is suggested to ensure that the combination does not have harmful effects [13].

Both pyrimethamine and sulphadoxine cross the placental barrier and also pass into breast milk [50]. Sulphonamides could theoretically increase the risk of kernicterus in the infant if given to a pregnant woman near term, due to the ability of sulphonamides to displace unconjugated bilirubin from albumin [51]. However, this has not actually been seen in clinical trials of IPTp, clinical treatment of cases of malaria or in the treatment of congenital toxoplasmosis (which uses pyrimethamine, sulphadiazine and folinic acid) [51,91].

Drug interactions

Probenecid

Probenecid is a ucosuric agent that inhibits the tubular secretion of organic anion derivatives. These organic anions (such as penicillin and analogs), which are primarily derivatives of carboxylic acid (DCA), are secreted in the kidney by organic anion transporters (OATs). Probenecid, which is also a DCA, interacts with these OATs, leading to a decrease in DCA secretion [92,93]. Thus, the mechanism of action of probenecid depends on the inhibition of OATs, reducing the secretion of DCA. Most of the drugs reported in the list below are organic anion compounds that are secreted through OATs, hence their interaction with probenecid. In the next section, we detail specific probenecid-drug interaction.

List of drugs whose concentration or effects are increased by probenecid

- **Antibacterials:** Penicillins, Cephalosporins, Carbapenems, Quinolones, Dapsone, Rifampin, Tazobactam
- **Antivirals:** Ganciclovir, Valganciclovir, Oseltamivir, Peramavir
- **Antiretrovirals:** Zalcitabine, Zidovudine
- Methotrexate
- Acetaminophen
- **Non-steroidal anti-inflammatory drugs:** Indomethacin, Ketoprofen, Ketorolac, Naproxen, Zomepirac
- **Benzodiazepines:** Lorazepam, Midazolam, Nitrazepam
- Chlorothiazide (thiazide)
- **Loop Diuretics:** Bumetanide, Furosemide
- Mycophenolate
- **Theophylline Derivatives:** Dyphylline, Enprofylline but NOT Aminophylline or Theophylline

Table 1 Reports of probenecid use during pregnancy

Author	Study	N	Treatment	Timing of Treatment	SAEs	Infant Outcome
Cavenee et al. [84]	Treatment of gonorrhoea in pregnancy	123	Amoxicillin 3 gm + probenecid 1 gm	64 patients (25%) treated in 1st trimester of pregnancy	None, one woman reported vomiting several hours after taking the drug	71 infants were evaluated, 14 treated < 14 week, 1 major malformation (7%), 4 minor malformations (29%); 57 > 14 week, 0 major and 10 minor malformations (18%), overall 1% major and 20% minor malformations, not statistically different from other groups
Adelson et al. [85]	Treatment of urinary tract infections in pregnancy	98	Ampicillin 3.5 gm + probenecid 1 gm	Not stated	3 patients developed candidal vulvovaginitis, 3 patients developed diarrhoea	Not stated
Brown et al. [86]	Renal clearance of oestrogen in pregnancy	9	Probenecid 2.5 gm	Last 6 weeks of pregnancy	None reported	No foetal deaths or stillbirths
Lee et al. [87]	Gout and pregnancy	1	Probenecid 1 gm to 3 gm daily throughout pregnancy	Throughout pregnancy	Anaemia thought related to renal disease	Healthy infant
Weingold et al. [88]	Gout and pregnancy	1	Colchicine and probenecid	Throughout 1st pregnancy and for the first 14 weeks of 2 nd pregnancy	Mild anaemia	1st pregnancy: infant died on DOL4 due to hyaline membrane disease 2 nd pregnancy: healthy infant
Goodrich [55]	Gonorrhoea and pregnancy	163	Penicillin G 4.8 × 10 ⁶ U (n = 158) or ampicillin (n = 5) + probenecid 1 gm	Not stated	None reported	Not stated
Schackis [89]	Hypertension and pre-eclampsia	20*	Probenecid 250 mg twice daily for 7 days	26-32 weeks gestation	No side-effects to probenecid were recorded	There were 3 intrauterine foetal deaths: 1 from an abruptio placenta (> 1 kg) in the probenecid group and 2 from suspected placental insufficiency (both < 1 kg): 1 each in the probenecid and placebo group.
Czaczkas et al. [90]	Pre-eclampsia, eclampsia	18†	Probenecid 0.5 gm 3 times daily for 5-6 days	Not stated	None reported	Not stated

*20 women treated and an additional 20 untreated controls

†15 women with pre-eclampsia + 3 pregnant controls without pre-eclampsia

- **Sulphonylureas:** Glimepiride, Glyburide
- Nitrofurantoin
- Apazone
- Entacapone
- Famotidine
- Pemetrexed
- Pralatrexate
- Sodium Phenylacetate, Sodium Benzoate

Probenecid is antagonized by both salicylates and pyrazinamide [31]. Allopurinol decreases the serum concentration of probenecid while probenecid increases that of allopurinol. However, the clinical significance of this is probably minimal [31]. Probenecid decreases the natriuretic effect of piretanide [31]. Probenecid increases the metabolism of phenprocoumon, leading to decreased AUC [94]. Probenecid has a nephroprotective effect when co-administered with cidofovir, but without significantly altering plasma

blood levels [94]. It is a weak inhibitor of CYP2C19 and blocks the renal transport of many compounds including many classes of antibiotics, antivirals, and NSAIDs leading to an increase in their mean plasma elimination half-life that can lead to increased plasma concentrations [31]. In some cases, this may increase the potential for toxicity.

Sulphadoxine-pyrimethamine

Neither sulphadoxine nor pyrimethine, nor their primary metabolites, are DCA [95,96], thus the mechanisms of secretion of these two drugs are not likely to involve OATs. Therefore, their pharmacokinetics would not be affected by probenecid. In support of this hypothesis, the clinical evaluation of probenecid with SP did not indicate any increase in sulfadoxine or pyrimethamine toxicity [19]. However, further investigations need to be carried out to establish the pharmacokinetics, safety, and efficacy of probenecid + SP, before this combination could be used routinely for IPTp.

SP should not be used in combination with other antifolates (i.e. trimethoprim), sulphonamides, or other agents associated with myelosuppression, as this can increase the risk of bone marrow suppression (Table 2). The concurrent use of gold salts and anti-malarial agents is also contraindicated due to an increased risk of blood dyscrasias. Sulphadoxine decreases the serum concentration of cyclosporine while enhancing its nephrotoxic effect. Potassium P-aminobenzoate and its derivatives (Procaine, benzocaine, and tetracaine) can decrease the therapeutic effect of sulphadoxine, while folate derivatives can decrease the therapeutic effect of pyrimethamine. The concomitant administration of antacids or absorbent anti-diarrhoeals may significantly reduce the bioavailability of pyrimethamine by reducing its absorption. Pyrimethamine inhibits CYP2C9 and CYP 2D6, and may therefore interact with other compounds, which are metabolized via these pathways (Table 3).

SP-IPTp works both through clearance of existing asymptomatic infections as well as prophylactically by preventing new infections [1]. The prophylactic effect of SP is believed to be of primary importance [1]. Due to

the long half-life of SP, its parasitocidal drug levels are sustained for weeks in the case of sensitive parasites, providing a prolonged period of prophylaxis. As parasite resistance to SP increases, the period of prophylactic efficacy becomes shorter [21]. Even if probenecid can increase the concentration of SP, given the very short half-life of probenecid (less than 20 h) compared to SP (approximately 100 h), this effect is unlikely to be sustained. Therefore, while the addition of a single dose of probenecid to SP may be useful for treatment, it is unclear to what extent it will provide a prolonged period of prophylaxis in the context of IPTp. Multiple doses of probenecid may be needed to provide a sustained benefit of SP-IPTp. However, a multiple-dose regimen would be less ideal as compliance with such a regimen is likely to be low.

Conclusions

The antifolate SP is widely used for IPTp; it is the only drug currently recommended for IPTp by WHO and has been adopted as national policy in 37 countries worldwide, 33 of which are in the sub-Saharan region

Table 2 Drugs that interact with sulphadoxine

Drug	Effect of Interaction
Phenytoin	Serum hydantoin levels and risk of toxicity may be increased due to inhibition of hepatic metabolism by sulphadoxine
Sulphonylureas (Glimepiride, Glyburide)	The hypoglycemic potential of the sulphonylureas may be increased; the mechanism of this interaction is unknown.
Vitamin K antagonists (Coumadin, anisindione)	Co-administration with a sulphonamide may increase the plasma concentrations and hypoprothrombinemic effects of coumarin anticoagulants
Gold salts	Increase the risk of blood dyscrasias
Cyclosporine	Sulphadoxine decreases the serum concentration of cyclosporine while enhancing its nephrotoxic effect

Table 3 Drugs that interact with pyrimethamine

Drug	Effect of Interaction
Gold salts	Increased risk of blood dyscrasias
Methotrexate	Increased risk of bone marrow suppression
Dapsone	Folate antagonists may increase the likelihood of adverse hematologic reactions (e.g., agranulocytosis, anaemia)
Carvedilol	Possible for increased serum concentration of the S-carvedilol enantiomer
Phenothiazines	Anti-malarial agents may increase the serum concentration
Fesoterodine	Serum concentrations of the active metabolite may be increased
Nebivolol	Serum concentration may be increased
Zidovudine, abacavir, lamivudine	Increased risk of bone marrow suppression
Tamoxifen	Metabolism of Tamoxifen to the active metabolites may be decreased
Lorazepam	Increases risk of elevated liver function tests
Codeine	CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine, diminishing its therapeutic effect
Tramadol	CYP2D6 inhibitors may prevent the metabolic conversion to the active metabolite, diminishing its therapeutic effect
Antacids	Reduce the absorption of pyrimethamine (decreased bioavailability)

[97,98]. However, resistance of malaria parasites to SP has been increasing, and there is accumulating evidence from eastern Africa that the efficacy of SP-IPTp is declining. Therefore, new drugs and strategies are urgently needed. As malaria transmission declines, the risk associated with administering a drug to all pregnant women will no longer outweigh the potential benefit associated with preventing malaria, and it is likely that IPTp will be abandoned. In the interim, in vitro and in vivo data suggest that combining probenecid with SP significantly increases the efficacy of SP, and might therefore be a useful strategy in HIV-uninfected women until new drugs for IPTp are evaluated and deployed [13-16], although this combination may not be sufficiently efficacious in areas with a high degree of resistance. Although probenecid has been in use for many decades, very few data exist on its use in pregnancy; however, the available data suggests that it is safe. Prior to recommending this combination for widespread use, additional information is needed on its safety and pharmacokinetics in pregnancy, and given the difference in the half-lives of SP and probenecid, data are needed to determine the optimal dosing schedule. In addition, studies are needed to determine whether the increased dose of SP achieved by this combination improves the efficacy against partially resistant parasites. Mathematical modelling may be able to assist in this determination. Overall, available data on efficacy, safety and cost for these drugs necessitates further research into their combination for use in IPTp [48,55].

Abbreviations

SP: Sulphadoxine-pyrimethamine; IPTp: Intermittent preventive treatment in pregnancy; *dhps*: Dihydropteroate synthetase; *dhfr*: Dihydrofolate reductase; G6PD: Glucose-6-phosphatase dehydrogenase; MRP: Multidrug resistance-associated protein; AUC: Area under the curve; OAT: Organic anion transporter; DCA: Derivatives of carboxylic acid

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Disclaimer

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Authors' contributions

TK and AN were responsible for the concept of the manuscript. JG was responsible for the acquisition of data, interpretation of the data and writing the manuscript. SPK, LS, AN, and TK contributed to interpretation of the data and critically revised the paper. All authors have seen and approved the final version.

Competing interests

The authors declare that they have no competing interests.

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